Successful Integration of Distributed Drug Discovery (D3) Components: Computational, Synthetic, and Biological Evaluation of Phenylalanine Derivatives as Potential Biofilm Inhibitors

Milata M. Abraham [a]**, Jonathan M. LaCombe**[b]**,** Jon M Carnahan [a], Martin J. O'Donnell [a], William L. Scott[a], Ryan E. Denton[a], J. Geno Samaritoni[a], Richard Harper[a], Gregory G. Anderson[b], Kathleen A. Marrs[b], Barbara M. Coffey[b]
[a]IUPUI Department of Chemistry and Chemical Biology; [b]IUPUI Department of Biology.

Distributed Drug Discovery (D3) is a multidisciplinary approach to identifying molecules that exhibit activity in the treatment of neglected diseases such as malaria, leishmaniasis, and tuberculosis as well as recalcitrant cystic fibrosis (CF) airway infections. D3 seeks to accomplish this task by combining computational chemistry, synthetic chemistry, and biological screening all within an educational framework. Recent reports suggest that D-amino acids are effective in the disassembly and inhibition of bacterial biofilms, which are important for a number of bacterial infections, including those in the CF lung. Utilizing chemical drawing software, we constructed (enumerated) target phenylalanine derivatives from commercially available benzyl halides by substitution at the α position of an amino acid scaffold. A subset of these enumerated molecules was computationally selected for synthesis based on chemical properties. These compounds were synthesized using simple, solid-phase techniques in an undergraduate organic chemistry laboratory class. The resulting racemic unnatural amino acid derivatives were then screened for activity in a biofilm assay. The results show biofilm inhibition with synthesized phenylalanine derivatives. Analysis of the results reveals a trend between lipophilicity and the degree of biofilm inhibition. These new molecules may lead to an avenue for therapy for those CF individuals suffering with bacterial lung infection. As a part of the undergraduate curriculum, this work provides the first example of D3-linked undergraduate student computational analysis, synthesis, and biological evaluation.

Mentors: Martin J. O'Donnell, William L. Scott, Department of Chemistry and Chemical Biology, School of Science, IUPUI; Kathleen A. Marrs, Gregory Anderson, Department of Biology, School of Science, IUPUI.